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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,113	10/17/2001	Gabriel Lopez-Berestein	UTSC:660US/SLH	9331
7590 02/20/2004			EXAMINER	
FULBRIGHT & JAWORSKI L.L.P. A REGISTERED LIMITED LIABILITY PARTNERSHIP Suite 2400 600 Congress Avenue Austin, TX 78701			KISHORE, GOLLAMUDI S	
			ART UNIT	PAPER NUMBER
			1615	
DATE MAILED: 02/20/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/982,113

Applicant(s)

LOPEZ-BERESTEIN ET AL.

Examiner

Gollamudi S Kishore, PhD

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11-20-03.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-141 is/are pending in the application.
- 4a) Of the above claim(s) 61-130 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 54-60 and 131-141 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

The response filed on 10-20-03 is acknowledged.

Claims included in the prosecution are 56-60 and 131-141.

Claim Rejections - 35 USC ' 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 54-56 and 131-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (5,811,119) in view of Ulukaya (Cancer Treatment Reviews, 25, pp. 229-235, 1999 of record).

Mehta discloses a method of treatment of cancer using liposomal retinoid. The liposomes are made from the claimed combination of dimyristoyl phosphatidyl choline and the intercalation promoter, soybean oil (note the abstract, col. 3, lines 16-21; col. 6, line 24 through col. 7, line 31; Examples, in particular Examples 1, 5, 6 and 9. Although

Art Unit: 1615

in Mehta, the invention is exemplified using retinoic acid, according to Mehta on col. 2, line 60 et seq., the term includes all retinoids.

Mehta however, does not specifically teach 4 hydroxyphenyl retinamide.

Ulukaya while disclosing the relationship between 4 hydroxyphenyl retinamide and cancer, teaches that this retinoid has fewer side effects compared to naturally occurring retinoids and that it seems to induce apoptosis via different pathway from classical retinoids (note the abstract).

The use of 4-hydroxyphenyl retinamide as the specific retinoid in the teachings of Mehta would have been obvious to one of ordinary skill in the art since Mehta teaches the use of any retinoid and Ulukaya teaches that this retinoid has fewer side effects compared to naturally occurring retinoids and induces apoptosis via different pathway from classical retinoids. The mode of administration recited in the added claims is deemed to be a manipulatable parameter. The criticality of the ratios and the amounts of water in the added claims is not readily apparent to the examiner in the absence of showing of unexpected results.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicant argues that at best, the prior art of Mehta only renders it 'obvious to try'. This argument is not found to be persuasive since Mehta teaches the applicability of his invention to several retinoids and exemplifies his invention using a specific retinoid and therefore, the reference is not just an 'obvious to try' reference. Applicant argues that Ulukaya teaches away since he teaches that 4-HPR has properties that distinguish(es) it from naturally occurring retinoids, including the fact that

Art Unit: 1615

it apparently exerts its clinical effects by a different pathway from classical retinoids.

First of all, Ulukaya only speculates the mechanism of action. In the abstract section, the statement made by Ulukaya is "Although the mechanism by which fenretinide acts is not entirely known it is considered to be a promising drug ----". Irrespective of the mechanism by which acts, it is the position of the examiner that one of ordinary skill in the art would be motivated to use 4-HPR because of its ability to induce cell death even in ATRA –resistant cell lines as taught by Ulukaya. Applicant argues that Mehta proposes the use of lipid formulations is for the purpose of 'reduced toxicity' and yet Ulukaya teaches that the 4-HPR in and of itself solves the toxicity problem and therefore there is no motivation from Ulukaya or Mehta to provide a lipid based formulation of 4-HPR. This argument is not found to be persuasive since reduction of drug toxicity by is only one of Mehta's reasons for using liposomes. On col. 2, lines 5-18, Mehta clearly states that liposomal format is a useful one for controlling the topography of drug distribution in vivo. Mehta further states, "This, in essence, involves attaining a high concentration and/or long duration of drug action at a target (e.g. a tumor) site where beneficial effects may occur, ----". Applicant's arguments thus, are not found to be persuasive and the rejection is maintained.

3. Claims 54-60 and 131-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (5,811,119) in view of Minton (5,008,291) or Zeligs (6,093,706) by themselves OR vice versa: that is, Minton (5,008,291), or Zeligs (6,093,706) in view of Mehta (5,811,119).

Mehta discloses a method of treatment of cancer using liposomal retinoid. The liposomes are made from the claimed combination of dimyristoyl phosphatidyl choline and the intercalation promoter, soybean oil (note the abstract, col. 3, lines 16-21; col. 6, line 24 through col. 7, line 31; Examples, in particular Examples 1, 5, 6 and 9. Although in Mehta, the invention is exemplified using retinoic acid, according to Mehta on col. 2, line 60 et seq., the term includes all retinoids.

Minton in 291 teaches that a combination method for achieving a very high degree of chemotherapeutic activity through a synergistic combination of a low sub optimal dose of calcium glucarate (anti-carcinogen) and a sub optimal dose of 4-hydroxyphenyl retinamide. One of the cancers studied is mammary cancer (abstract; col.4, line 23 through col. 6, line 41; Examples). What is lacking in Minton is the use of liposomes as the sustained release carriers for the combination. However, Minton on col. 13, lines 17 and 18 suggests the use of sustained or continuous release formulations.

Zeligs teaches a combination treatment of diseases such as squamous cell carcinoma using 4-hydroxyphenyl retinamide and dehydroepiandrosterone. The combination is administered in the form of liposomes (abstract, col. 5, line 28; col. 6, line 60; Example 3; claims 46 and 55). What is lacking in Zeligs= liposomes is the use of DMPC as the phospholipid and the inclusion of soybean oil.

It would have been obvious to one of ordinary skill in the art to use 4-hydroxyphenyl retinamide as the specific retinoid in the teachings of Mehta since Mehta teaches the use of any retinoid and the references of Minton and Zeligs show the

Art Unit: 1615

effectiveness of this retinoid in combination with other active agents which includes synergism as noted from Minton. Alternately, the use of liposomes containing DMPC and soybean oil of Mehta as the sustained release carriers for the formulations of Minton, or Zeligs would have been obvious to one of ordinary skill in the art since this combination of DMPC and the intercalation promoter, soybean oil is very effective for the delivery of retinoids in cancer treatment process as taught by Mehta. The mode of administration recited in the added claims is deemed to be a manipulatable parameter. The criticality of the ratios and the amounts of water in the added claims is not readily apparent to the examiner in the absence of showing of unexpected results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant appears to question the relevancy of Minton's disclosure to DMPC/SO/water formulations. Applicant argues that Minton simply teaches that one can prepare sustained release formulations of the 4-HPR and calcium gluconate. Minton not only teaches the chemotherapeutic action of 4HPR, but also the synergistic effect of 4 HPR when combined with another anti-cancer agent. Instant claims 57-61 claim a combination of active agents. One of ordinary skill in the art would be motivated to combine an additional active agent along with 4 HPR with an expectation of obtaining at least an additive effect based on the teachings of Minton. Similar is the case with the reference of Zelig. Applicant's arguments regarding high encapsulation efficiency in instant invention (page 83 according to applicant) and lack of such in Mehta (Table 1 according to applicant) are not persuasive since Table 1 in Mehta shows high encapsulation of the active agent (even 90.7) and instant results on page 83 also show

Art Unit: 1615

variation between 60 to 96.5. With regard to applicant's arguments that Mehta discloses reconstitution of already formed liposomes in an aqueous medium and it does not appear that there is any teaching of actually forming liposomes using water with the lipids, the examiner points out that the claims are method claims based on a product and not method preparation claims. In essence, instant claims do not recite the claimed differences in the process of preparation.

4. Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (5,811,119) in view of Ulukaya (Cancer Treatment Reviews, 25, pp. 229-235, 1999 of record as set forth above, further in view of Minton (5,008,291), or Zeligs (6,093,706).

The teachings of Mehta, Ulukaya, Minton and Zeligs have been discussed above. What is lacking in Mehta is the teaching of the administration the composition in combination with an additional agent.

As pointed out above, Minton, and Zeligs teach the combination of 4-hydroxyphenyl retinamide with glucanolactone and DHEA respectively.

It would have been obvious to one of ordinary skill in the art to include an additional agent in the compositions of Mehta since the references of Minton and Zeligs show the effectiveness of this retinoid in combination with other active agents which includes synergism as noted from Minton.

Applicant provides no specific arguments with regard to this rejection. The examiner has already addressed the arguments pertaining to individual references.

Art Unit: 1615

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1615

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK